# THE THERAPEUTIC ROLE OF PROCAINE AND ITS DERIVATIVES*

E. A. ROVENSTINE

Professor of Anesthesia, New York University College of Medicine and Director of Anesthesia, Bellevue Hospital

E. M. PAPPER

Assistant Professor of Anesthesia, New York University College of Medicine

DURING THE 43 years that have elapsed since Einhorn announced the synthesis of p-amino-benzoyl-diethylamino-ethanol, the drug now known as procaine, it has become fully established as the most popular agent for local, regional and spinal anesthesia. Any drug with such wide usage is necessarily the object of many laboratory and clinical experiments designed to determine conclusively its pharmacological properties, its toxicity and to define its optimum use clinically. That the desired goal of such researches has not been achieved is now obvious from the considerable new material being added to our knowledge of procaine in the very recent past and at the present time. The most significant of these later experiments in both the laboratory and clinic are associated with the use of procaine administered intravenously.

Procaine was injected first into the veins of man 40 years ago.[1] This was done with a tourniquet in place and its object was to produce anesthesia of the extremities. The practice was soon abandoned. The present widespread use of intravenous procaine is a recent addition to therapy. It is readily understandable why intravenous procaine was so long avoided. Standard textbooks and other medical literature repeatedly pointed out the real danger of delirium, convulsions and death following the injection of procaine directly into the vascular system under any circumstances. There were numerous reports describing fatal convulsions in man after comparatively small amounts of procaine were inadvertently injected intravenously.

* From the Department of Anesthesia, New York University College of Medicine and the Division of Anesthesia, Bellevue Hospital, New York City.

Given October 12, 1948 before the 21st Graduate Fortnight of The New York Academy of Medicine.

In our laboratories (1940) procaine was given intravenously to anesthetized dogs during experiments undertaken to determine a means for protection against cardiac arrhythmias produced by injecting epinephrine.[2, 3] A definite protection was demonstrated and later similar results were observed in humans. This was substantiated during the war by Burstein when an opportunity was afforded for more extensive and better controlled observations in a busy army thoracic surgery center.[4] The administration of intravenous procaine in large amounts in the anesthetized patient was followed by successful attempts to use the drug therapeutically in unanesthetized individuals.[5, 6, 7]

It is now determined from extensive clinical observation that comparatively large amounts of procaine can be tolerated by man when given slowly by vein. With this knowledge intravenous procaine has been "tried" as a therapeutic agent for a surprisingly large number of unrelated clinical conditions. It has been used as an analgesic, for vasodilatation, to relieve muscle spasm, to diminish cardiac irritability and for an anti-histamine effect.

## Clinical Application

The empirical application of intravenous procaine in clinical medicine has gained momentum without a well-defined fundamental basis for its action. This circumstance has occasioned a wide discrepancy in the reported results from its use. There is much speculation concerning the precise mechanism or mechanisms to explain the effects observed when the drug is administered as a therapeutic agent.

The essential action of procaine has been described as a direct one on the arterioles and capillaries with widespread dilatation. Although there is clinical evidence that peripheral circulatory dilatation occurs, conclusive experimental support in humans is lacking. Direct measurements of surface temperature should show an increase if capillaries in the skin are dilated. Our own efforts to establish this in man have given negative results. Dilatation probably could be produced if a large enough amount of procaine could be given intravenously. The serious toxic reactions to such doses constitute a barrier.

Graubard, Robertazzi and Peterson[8] gave procaine intravenously to relieve the muscle spasm of poliomyelitis. They were optimistic with the results and others have made similar observations. No explanation for this effect has been established.

There is ample clinical evidence that cardiac irritability is reduced with procaine applied topically to the myocardium or given intravenously.[2, 9] This effect is firmly established and is in accord with theoretical considerations in that there is a similarity in chemical configuration with quinidine, benadryl and other compounds which act as protoplasmic depressants upon the myocardium.

The anti-histamine action of procaine is not established by laboratory investigation although it has been successfully used to treat serum sickness.[10] This has been attributed to an anti-acetylcholine action. Harvey[11] has shown that procaine depresses the response of the terminal efferent fibers to acetylcholine and decreases production of acetylcholine at these sites. Conduction in nerve fibers may depend to some extent upon release and removal of acetylcholine, a process which is inhibited by the neutralizing action of procaine.

The reported analgesic effect of procaine given intravenously has provoked considerable speculation as to the mechanism involved. It has been suggested that it follows the leakage of procaine into the perivascular areas to reach the nerve endings through damaged capillaries. This can not be accepted until analysis of fluids at the site of injury are made. It was further suggested that analgesia may be the result of central action. This is supported by experiments on changes in pain threshold using the Hardy-Wolff-Goodell technique. Bigelow and Harrison,[12] using subcutaneous injections found a rise in pain threshold of about ⅓ of normal or the same range with therapeutic doses of acetylsalicylic acid. Using the drug intravenously, similar determinations were made here.[13] It follows that the clinical results reported are not consistent with the elevations of pain threshold observed. Either the concept of pain threshold is not so important in the evaluation of an analgesic drug, or the therapeutic benefits are the result of some other process.

In the wide use of procaine intravenously, more consistent agreement on its effectiveness has been demonstrated in the control of pain following trauma. There is general agreement that patients with fractures and other musculo-skeletal injuries experience less pain when procaine is administered.[8] In these groups are those with surgical trauma. Although this use of procaine has been established, it should be pointed out that pain syndromes of this nature have a wide individual variation and constitute a clinical group extremely difficult to evaluate in deter-

mining the effectiveness of analgesics. This is true also of the patients with pain from inflammatory reactions. In the latter group, optimistic results are reported in treating pain in the arthritides, neuritides and vascular disease. Considerable evidence has accumulated to warrant the use of intravenous procaine for burns, pruritus, and allergic skin reactions. Intravenous procaine has been used as an analgesic during parturition and for minor surgical procedures. One may say conservatively now that procaine may be an analgesic of consequence for patients with pain associated with trauma and inflammation. The favorable clinical application in other pain circumstances has not been established to the extent that it surpasses other means for effective therapy.

The evidence accumulated on the ability of procaine to correct alterations of cardiac rhythm is sufficient to establish it as the present drug of choice. This statement is qualified for the anesthetized patient only, since the amount needed in patients without the protection of anesthesia is too toxic for clinical usage. During anesthesia, procaine is of questioned prophylactic value, but finds its indication in the reversal of an abnormal rhythm. This should be further qualified to include the ventricular arrhythmias only. It is the firm conviction here that this latter use of procaine is more effectively accomplished when a single dose is given rapidly at the time its need is obvious. The aim is to provide the heart with an effective dose for a brief time during which irregularities of rhythm may be abolished.

## Techniques

In efforts to determine the amount of procaine to produce maximum analgesia and other therapeutic effects, various recommendations have been made. In this regard there are two goals: to establish analgesia and to avoid aggravating or serious toxic reactions. Graubard and his associates[8] suggested a "procaine unit" calculated at 4 mgm./Kg. of body weight to be given in 0.1 per cent solution in isotonic saline in 20 minutes. Such calculations would be more accurate if obesity were not a factor and if they were determined by an accurate analysis of the rate of destruction of the drug. It is true that this calculated dose is tolerated without toxic manifestations and this may follow the fact that its destruction occurs in plasma at a rate almost as rapid as it is being administered. The clinical impression from the experience here is that effective intravenous procaine medication can be had by an amount

of the drug that continuously provides mild toxic manifestations. These include such symptoms as apprehension, metallic taste, slight nausea, vertigo and a feeling of warmth. If more serious symptoms of muscle tremors, delirium and convulsions are produced, the drug must be discontinued to avoid failure of the circulation and respiration.

Procaine may be administered to unanesthetized patients in 0.2 per cent solution for rapid effect and to avoid large amounts of fluid if this is desirable. The rate that it should be given is widely variable with individuals and must be determined with the criteria of effective analgesia in the light of mild toxic manifestations as a guide.

The most favorable effects in the treatment of arrhythmias in the anesthetized individual have followed the rapid injection of 100 mgm. of the 1.0 per cent solution.

Vitamin C is often given with intravenous procaine and many clinicians use the barbiturates for their prophylaxis against toxic reactions.

## Mechanism of Action

Notwithstanding this vast accumulation of clinical experience with intravenous procaine, the mechanism of action, distribution in the tissues and its precise fate is still undetermined. It would seem that this fundamental knowledge should be available before the precise role of procaine in therapy can be determined accurately. Consequently a systematic study of the pharmacology of procaine has been undertaken in our laboratories. More detailed reports of these studies are available elsewhere but essentially the initial effort was to devise chemical methods for the identification of procaine and the products of its hydrolysis.[14] With these methods it was learned that an enzyme present in plasma was largely responsible for the almost instantaneous destruction of procaine to its metabolites, di-ethyl-amino-ethanol and para-amino-benzoic acid. In addition to establishing the manner of disposition of procaine in vivo, it was desirable to determine whether the observed toxic effects were associated with procaine itself or some product of its normal degradation. It seemed entirely possible that the therapeutic action of procaine could be exerted by a metabolite which was less toxic than the parent drug or if this were not the case, that procaine itself could be altered by chemical substitution in the molecule to make a more stable and effective drug.

In studies upon normal man, Brodie and his coworkers[14] demon-

strated that procaine is very rapidly hydrolyzed after intravenous administration and that urinary excretion is almost negligible as a method of disposition of the injected drug. Since 70 to 95 per cent of the para-amino-benzoic acid (free and conjugated) in procaine is recovered in the urine, it was apparent that this material was largely unaltered in the body. On the other hand, amounts of di-ethyl-amino-ethanol equivalent to 20 to 35 per cent of the original procaine can be isolated from the urine. When para-amino-benzoic acid and di-ethyl-amino-ethanol are injected as such, quantitative recovery in the urine is identical with that described when these substances are administered in the esterified form as procaine. It is evident, therefore, that the di-ethyl-amino-ethanol product of the hydrolysis of procaine is further metabolized in vivo in a manner as yet undetermined.

The fact that the concentration of procaine in the plasma does not increase with continuous intravenous administration while that of the alcohol metabolite does, as clinical effects are noted, suggests that the latter may be the pharmacologically active agent rather than the parent drug. The role of para-amino-benzoic acid has not been completely investigated, but the previously known behavior of this substance and the results of some few experiments offers little support for the possibility that it exerts many of the actions commonly attributed to procaine.

It seemed desirable, therefore, to investigate the pharmacological effects of di-ethyl-amino-ethanol upon man and laboratory animals. Observations early in the course of these studies indicated that the toxic effects were qualitatively similar to procaine, but large doses could be given intravenously before these were apparent. The margin of safety was significantly greater than with procaine. The relative lack of toxicity of this material and its greater flexibility with regard to dosage, pointed the way to a comparison with the orthodox actions of procaine. Comparisons were directed toward the properties which have been reported for procaine.

## Di-ethyl-amino-ethanol Studies

Among the early efforts to compare the effects of the alcohol metabolite of procaine with the parent drug were those directed toward its ability to diminish cardiac irritability. This action which may be due to a protoplasmic depression of conductivity in cardiac muscle has been

studied in anesthetized animals and unanesthetized man. Di-ethyl-amino-ethanol is somewhat more efficient than procaine, although in larger doses, in reversing cyclopropane-epinephrine ventricular arrhythmias in the dog to sinus rhythm. The therapeutic benefit of the alcohol persists for longer periods than that produced by procaine. In unanesthetized humans the experience to date, although not extensive or conclusive, suggests that ventricular arrhythmias may be suppressed often when comparatively large doses of the alcohol (0.5 to 5.0 gms.) are given rapidly by vein. In another report, Rosenberg and his associates[15] describe 14 patients with ventricular extrasystole 13 of whom had normal rhythm after receiving di-ethyl-amino-alcohol. Another 8 patients with ventricular tachycardia were similarly treated with a restoration of pre-existing rhythm following in 6 of them. This effect on the specific tissues of the heart varies in duration. Similar results were unobtainable when attempts were made to treat supraventricular arrhythmias.

Di-ethyl-amino-ethanol has local anesthetic properties. Using local intracutaneous injections it was determined that the drug produced definite anesthesia for 20 to 30 minutes when a 10 per cent concentration was employed. No anesthesia was obtained when weaker solutions (1.0 per cent) were used.

The effects of di-ethyl-amino-ethanol upon the pain threshold were studied by a modified Hardy-Wolff-Goodell technique. Four grams of the drug given rapidly produced a definite, although slight, elevation of threshold. This elevation was within the range to be had with therapeutic doses of acetyl-salicylic acid and is inconsistent with clinical observations as is true with similar studies with procaine.

Skin temperature determinations were made before and after di-ethyl-amino-ethanol was given intravenously to determine vasodilatation in the skin and its actions upon smooth muscle. Amounts of 3.0 to 4.0 grams regularly produced an increase in skin temperatures of 3 to 9°C.[16] This definite effect was not repeated here with non-toxic amounts of procaine and suggests the alcohol more effective than the ester in overcoming vascular spasm.

The systemic analgesic effects of di-ethyl-amino-ethanol are similar to those that may be anticipated from intravenous procaine. The opportunities to complete significant studies have not been available during the short period the drug has been under observation. The early impression is that di-ethyl-amino-ethanol in relatively large doses is equally

efficient with procaine as an analgesic. It has the advantage of less troublesome administration and almost none of the toxic manifestations.

When toxic reactions from di-ethyl-amino-ethanol were observed they followed rapid injections of large amounts of the drug. These were similar to the mild reactions from procaine and are transient. Vertigo, slurred speech, a feeling of warmth, nausea and mild retching have occurred. Mild hypotension of short duration has also been determined. It is safe to say, however, that the serious toxic effects from procaine are not a hazard when its metabolite, di-ethyl-amino-ethanol is used therapeutically.

## Summary

Intravenous procaine is now popular therapy for many unrelated clinical conditions. It is used for analgesia, for vasodilatation, to depress cardiac irritability and for an anti-histamine effect. The mechanisms for this variety of activities are unknown. Some of those suggested are discussed.

The technique for administering procaine intravenously is suggested.

One of the metabolites of procaine, di-ethyl-amino-ethanol has been used experimentally and clinically as a substitute for the parent drug. The results presently obtained from these studies are outlined.

## *REFERENCES*

1. Bier, A. Ueber Venenanästhesie, *Berl. klin. Wchnsch.*, 1909, *46*:477.
2. Burstein, C. L. and Marangoni, B. A. Protecting action of procaine against ventricular fibrillation induced by epinephrine during cyclopropane anesthesia, *Proc. Soc. Exper. Biol. & Med.*, 1940, *43*:210.
3. Burstein, C. L., Marangoni, B. A., DeGraff, A. C. and Rovenstine, E. A. Laboratory studies on prophylaxis and treatment of ventricular-fibrillation induced by epinephrine during cyclopropane anesthesia, *Anesthesiology*, 1940, *1*:167.
4. Burstein, C. L. Treatment of acute arrhythmias during anesthesia by intravenous procaine, *Anesthesiology*, 1946, *7*:113.
5. Gordon, R. A. Intravenous novocaine for analgesia in burns (preliminary report), *Canad. M.A.J.*, 1943, *49*:478.
6. McLachlin, J. A. Intravenous use of novocaine as substitute for morphine in postoperative care, *Canad. M.A.J.*, 1945, *52*:383.
7. Allen, F. M. Intravenous obstetrical anesthesia; preliminary report, *Am. J. Surg.*, 1945, *70*:283.
8. Graubard, D. J., Robertazzi, R. N. and Peterson, M. C. Intravenous procaine; a preliminary report, *New York State J. Med.*, 1947, *47*:2187.
9. Beck, C. S. and Mautz, F. R. Control of heart beat by surgeon with special reference to ventricular fibrillation occurring during operation, *Ann. Surg.*, 1937, *106*:525.
10. State, D. and Wangensteen, O. H. Procaine intravenously in treatment of de-

layed serum sickness, *J.A.M.A.*, 1946, *130*:990.

11. Harvey, A. M. Actions of procaine on neuro-muscular transmission, *Bull. Johns Hopkins Hosp.*, 1939, *65*:223.
12. Bigelow, N. and Harrison, I. General analgesic effects of procaine, *J. Pharmacol. & Exper. Therap.*, 1944, *81*:368.
13. Papper, E. M., Brodie, B. B., Lief, P. A. and Rovenstine, E. A. Studies in the pharmacologic properties of procaine and di-ethyl-amino-ethanol, *New York State J. Med.*, 1948, *48*:1711.
14. Brodie, B. B., Lief, P. A. and Poet, R. Fate of procaine in man following its intravenous administration, *J. Pharmacol. & Exper. Therap., in press.*
15. Rosenberg, B., Kayden, H. J., Lief, P. A., Mark, L. C., Steele, J. M. and Brodie, B. B. Studies on diethyl-amino-ethanol; physiological disposition and action in cardiac arrhythmias, *J. Pharmacol & Exper. Therap.*, 1949, *95*:18.
16. Redisch, W., Sands, G. W. and Sheckman, W. *Personal communication.*